RULE 53 (37 C.F.R. 1.63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

a below named inventor, I hereby declare that my residence, post office address and critzenship are as stated below next to my name, and I believe I am the original, first and sole inventor (If only one name is listed below) or an original, first and joint inventor (if plural names—are listed below) of the subject matter which is claimed and for which a patient is sought on the invention entitled:

the specification of which (check applicable box(s)): It statistics will be a statistic of the statistic	subject m	atter which is claimed and	EPIDIDYM	IS-SPECIFIC RECEPTO	R PROTEL	N	
as us attached hereto was filed as PCT international application No. 35-128) was filed as PCT international application was amended on I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to be paterability of this application in accordance with 37 C.F.R. 1-58. I hereby claim foreign principly benefits under 35 U.S.C. 19369 of any foreign application by any amendment referred to above. I acknowledge the duty to disclose information which is material to be paterability of this application in accordance with 37 C.F.R. 1-58. I hereby claim foreign principly benefits under 30 U.S.C. 19369 of any foreign application for patent or inventor's certificate having a filling date before that of the application on which principly actime to principly actime the benefit under 35 U.S.C. \$119(e) of any United States provisional applications(s) isseed below. **Principly Foreign Application Number** I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional applications(s) isseed below. **Principly Foreign Application Number** I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such principle applications in the matiner prevised by the first paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filling date of the paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filling date of the paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose and the principle of the claims of this application of the claims of this application of the claims of this application of the claims	the energi	ication of which (check ap				-	
was filed a PCT international application No. and (if application to Uniternational application No. and (if application to U.S. or PCT application) was amended to U.S. or PCT application) was amended to U.S. or PCT application in accordance with 37 C.F.R. 1.59. I hereby claim foreign princing benefits under 35 U.S.C. 119/365 of any foreign application for patient or inventors certificate having a filling state before that of the application on which printy is claimed or, if no priority is claimed, before the filling date of this application. Portory foreign Application(S). Application Number County Day/Month/Year Filed I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional applications) listed below. Date/Month/Year Filed I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional applications is listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112 (applications) and the national or PCT international filing date of this applications and the national or PCT international filing date of this applications and the national or PCT international filing date of this application. Prior U.S.JPCT Application(s): Day/Month/Year Filed I hereby declare that all statements made incentin of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements made with the knowledge that willful false statements and the like so made are punishable by fine or impressional true. I hereby declare that all statements made incentin of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowled		itached hereto					(Atty Okt. No. 35-126)
and (if applicable to U.S. or PCT application) was amended on I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment reterred to above. I acknowledge the duty to disclose information which is material to be patentiability of this application in accordance with 37 C.F.R. 1.58. I hereby claim foreign priority peenfits under 35 U.S.C. 113965 of any foreign policitation (in priority peenfits under 35 U.S.C. 113965 of any foreign policitation for patent or inventor's certificate having a filling date before that of the application on which priority is claimed or. If no priority is claimed, before the filling date of this application: I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional application(s) listed below. Policitation Number I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional application(s) listed below. Date/Month/Year Filled I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional applications in the manner arovided by the first paragraph of 35 to 10 J.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filling date of the prior applications and the national or PCT international filling date of this applications. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are Seleved to true; and further that these statements were made with the knowledge that willful false statements made on information and belief are Seleved to true; and further that these statements were made with the knowledge that willful false statements and the filling date of the same application or any patent itsue thereon. And hereby appoint MIXON & VANDERHYE F.C., 1100 Worth Glebe Angle authority, 27076, justing or personal patent issued thereon. And hereby appoint MIXON & VANDERHYE F.C. 1100 Wort	50 was	s filed on		as U.S. Application :	Senai No.		(")
I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to be patentability of this application in accordance with 37 C.F.R. 1.98. I hereby claim foreign priority benefits under 35 U.S.C. 119786 of any foreign socicitations for patent or inventor's certificate below and have also identified below any friengin patientation for patent or inventor's certificate below and have also identified below any friengin patientation for patent or inventor's certificate having a filling date before that of the application on which priority Foreign Application for patent or inventor's certificate having a filling date before that of the application on which priority Foreign Application for the claims of the priority Foreign Application Number Country Day/Month/Year Filed I hereby claim the benefit under 35 U.S.C. \$119(e) of any United States provisional applications is steed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such pior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.58 which occurred between the filling date of the prior U.S.PCT Application (FT International filling date of this application). Prior U.S.PCT Application(s): Prior U.S.PCT Application(s): Day/Month/Year Filed I hereby declare that all statements made horein of my own knowledge are time and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful falls statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful falls statements made on information and belief are believed to be true; and further that these statements were		fled as PCT Internationa	l application No.			cn	
Ineraby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment reterred to above. I acknowledge the duty to disclose information which is material to be pateriability of this application in accordance with 37 C.F.R. 1.95. I hendry claim foreign priority peerflist under 35 U.S.C. 137956 of any foreign papilication on which priority is claimed or. If an application is application in Number I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional applications() listed below.	and /K and	nlicable to U.S. or PCT and	olication) was amended or	1			
amendment reterred to above. I acknowledge his duty to disclose moder 35 U.S.C. 119/36 of any foreign application of memoral certificate with 37 C.F.R. 1.58. I hereby claim foreign principly benefits under 35 U.S.C. 119/36 of any foreign application or which principly is claimed of in opinity is claimed and in opinity is claimed, before the filling date of this application. Principly Foreign Application(s): Day/Month/Year Filed							
I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below. Date/Month/Year Filled I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112.1 acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.59 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application. Prior U.S.PCT Application(s): Application Serial No. Day/Month/Year Filed Day/Month/Year Filed I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the function States Code and that such with raise statements may separatize the validity of the imprisonment, or both, under Section 1001 of Title 18 of the function States Code and that such with raise statements may separatize the validity of the imprisonment or any patent issued thereon. And hereby appoint NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8° Floor, Afrington, VA 22201-4714, belepance number (703) s14-a009 (to whom all communications are to be directed, 16° Rolling attempts (first) application and to transact all business in the Patent and Trademan Office connected therewith and with the resulting patent. Active 8°, C. Grayford, S. Syzoner, 27093; Leonard C. Mitchard, 29009; Duane M. Syers, 33353; Jerry H. Davidson, 33248; Waller and J. Kennan, 32106; Ryan H. Davidson, 33259; J. Store C. Sarthy, J. Wisson, 33489, Alan M. Kagen, 35178; William J. Griffin, 31250; Richard (Rist) Inventor	amendme with 37 C listed belo which price	ent referred to above. I act F.R. 1.58. I hereby claim ow and have also identified onty is claimed or, if no pri	knowledge the duty to disc foreign priority benefits un t helow any foreign applica	nder 35 U.S.C. 119/365 of ation for patent or inventor	any foreign	- annication(s) for	patent or inventor's certificate the before that of the application on
I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below. Date/Month/Year Filed I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.59 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application as defined in 37 C.F.R. 1.59 which occurred between the filing date of this applications and the national or PCT international filing date of this application as defined in 37 C.F.R. 1.59 which occurred between the filing date of this applications and the national or PCT international filing date of this application as defined in 37 C.F.R. 1.59 which occurred between the filing date of the prior u.S.PCT Applications and the national or PCT international filing date of this application and for the state of the United States Code and that set within false statements may leopardize the validity of the imprisonment. Or both, under Section (101 of Title 13 of the United States Code and that set within false statements may leopardize the validity of the application or any patent issued thereon. And I hereby appoint NIXON 8 VANDERNYE P.C., 1100 North Glebe Rd., 87 Pioor, Affingron, VA application or any patent issued thereon. And hereby appoint NIXON 8 VANDERNYE P.C., 1100 North Glebe Rd., 87 Pioor, Affingron, VA application and to transact all business in the Plant and Trademark Office address) individually and collectively my attorneys to prosecute this application and to transact all business in the Plant and Trademark Office connected therewith and with the evaluing patent. Antiny R. C.rawford, 25237, Larry S., Nixon, 2540, Robert A. Vandertye, 27076				Country			Day/Month/Year Filed
I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.58 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application. Prior U.S./PCT Application(s): Application Serial No. I hereby declare that all statements made horein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or be true; and further that these statements were made with the knowledge that willful false statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements made on information and belief are believed to be true; and further that these statements were made with the knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge are true and that all statements made on information and belief are believed to be directed and the like so made are punishable by fine or the true; and further that these statements were made with the knowledge are true and that all statements made on information and belief are believed to be directed and the like so made are punishable by fine or the true of a state and true that the state and true that all statements and the like so made are punishable by fine or the true	Applicati	ion Number		353,			
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2. Inventor's Signature: Inventor: Inventor: Residence: (city) Post Office Address: Residence: (city) Residence: (city) Post Office Address: Cate Set May 138	be true: imprison applicati 22201-4 address connecti 30184; F Spoonei	and further that these statement, or both, under Section or any patent issued the 714, telephone number (c) individually and collective ed therewith and with the recommendation of the first the section of the first t	ements were made with the identification 1001 of Title 18 of the ereon. And I hereby appoor 703) 816-4000 (to whome ely my attorneys to prosecresulting patent. Arthur Richard G. Besha. 22770; Mard, 29009; Duane M. Byo Wilson. 32955; J. Scott Drauist. 34776; Updeep S. Caroline (first) Hamburg Lutterothstr. 91, Hamb	United States Code and the NIXON & VANDERHY all communications are the this application and to Crawford, 25327, Larry Stark E. Nusbaum, 32348; ers, 33363; Jeffry H. Nels avidson, 33489; Alan M. Saill, 37334.* MI	hat such wi (E.P.C., 111) to be direct i transact al 3. Nixon, 29 Michael J. on, 30481: Kagen, 361	iful false statemer 00 North Glebe R. (1994), and the folio I business in the P. (1994). Robert A. Ve Keenan, 32106; B. Jonn R. Lastova. (1995). William J. Griff Da STERHOFF (4st)	its may jecpardize the validity of the d., 8th Floor, Arlington, VA wing attorneys thereof (of the same atent and Trademark Office inderlye, 27076; James T. Hosmer, ryan H. Davidson, 30251; Stanley C. 33149; H. Warren Burnam, Jr. 29366; in. 31260; Robert A. Molan, 29834; te:
2. Inventor's Signature: Inventor: Inventor: Residence: (city) Post Office Address: Residence: (city) Residence: (city) Post Office Address: Cate Set May 138							/
Inventor: Richard (first) MI (last) (citizenship) Residence: (city) Hamburg (state:country) Germany Post Office Address: Methfesselstr. 45. Hamburg, Germany		(Eib 000c)		1 : 1	1,	_	18+ Mas 1918
Inventor: Richard (first) MI (last) (citizenship) Residence: (city) Hamburg (state/country) Germany Post Office Address: Methfesselstr. 45. Hamburg, Germany	2	Inventor's Signature:	K	11 120	2.20		Reitigh
Residence: (city) Hamburg (state/country) Germany Post Office Address: Methfesselstr. 45. Hamburg, Germany	-		Richard				/ ==
Residence: (city) Hamburg (state/country) Germany Post Office Address: Methfesselstr. 45. Hamburg, Germany		mventor.		MI			(CILLES HOMP)
Post Office Address: Methfesselstr. 45. Hamburg, Germany		Residence: (city)	•		(state/cour	rty) Germany	· · · · · · · · · · · · · · · · · · ·
			Methfesselstr. 45. Han	nburg, Germany			
(Zip Code) 20231							
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COPY

RULE 63 (37 C.F.R. 1.63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION N THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if piural names, are listed below, of the subject matter which is claimed and for which a patent is sought on the invention entitled:

		EPIDID	YMIS-SPECIFIC RECEPTO	OR PROTE	N						
	ication of which (check a	opplicable box(s)):									
☐ is a ⊠ wa	attached hereto										
	s filed on	March 13, 1998	as U.S. Application	Senai No.	09/041.745	(Atty Dkt. No. 35-126)					
_	s filed as PCT Internation	· · · · · · · · · · · · · · · · · · ·			on						
and (if ap	plicable to U.S. or PCT a	pplication) was amended	on								
I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign applications for patent or inventor's certificate stad below and have also identified below any foreign application for patent or inventor's certificate naving a fling date before that of the accilication on which priority is claimed or, if no priority is claimed, before the filling date of this application:											
	oreign Application(s): on Number		Country			Day/Month/Year Filed					
I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) issted below Application Number. Date/Month/Year Filed											
I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112. I acknowledge the duty to disclose material information as defined in 37 C.F.A. 1 58 which occurred between the fit ng date of the order applications and the national or PCT international filling date of this application:											
Prior U.S	S./PCT Application(s):					Status: patented					
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be true: and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by the or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeccardize the validity of the application or any patent issued thereon. And I hereby appoint NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed), and the following attorneys thereof of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T. Hosmer. 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr. 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Alan M. Kagen, 36178; William J. Griffin, 31260; Robert A. Molan, 29834; B. J. Sadoff, 36663; James D. Berquist, 34776; Updeep S. Gill, 37334.* 1. Inventor's Signature:											
1.	Inventor's Signature:	<u> </u>	e (e//	00	Date:	German					
	Inventor:	Caroline (first)	MI	Ų3	(last)	(citizensh o)					
	Residence: (city)	Hamburg		state/countr	•	,					
	Post Office Address:	Lutterothstr. 91. Hami									
	(Zip Code)	20255	3,								
	ν -μ		21								
2.	Inventor's Signature:	- 210	Lett:	<u> </u>	Date:	1 t 2. 2000					
	Inventor:	Richard			IVELL	British					
		(first)	MI		(last)	(citizensnip)					
	Residence: (city)	Hamburg		state/count	ry) Germany						
	Post Office Address:	Methfesselstr. 45, Har	nburg, Germany								
	(Zip Code)	20257		/, -							
3.	Inventor's Signature:	(Print aux	" Kir Lland	//	Date	212.2000					
J.	Inventor's Signature:	Christiane		/	Kirchhoff	German					
	HIAGHIOL.	(first)	MI T	,	(last)	(citizensaip)					
	Residence: (city)	Bordesholm		(state/count	•	,,					
-	Post Office Address:		Veg 3. Bordesholm. Gern		•						
	(Zip Code)	D 24582									
	(r										
FOR AD	DITIONAL INVENTORS	check box 🔲 and atta	ach sheet with same info	mation and	d signature and date	for each.					

Assistant Commissioner for Patents Washington, DC 20231

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Osterfoff et al.

Atty. Ref.: 35-188

Serial No.

09/629,437

Group:

1646

Filed

July 13, 2000

Examiner: Ulm

For: EPIDIDYMIS-SPECIFIC RECEPTOR PROTEIN

DECLARATION UNDER RULE 132

- I, Dr. Ulrich Gottwald, hereby declare as follows:
- 1. I am employee of Schering AG and presently hold the position of Senior Scientist. A copy of my CV is attached.
- 2. I have read the above-identified application, including the claims, and the Office Action dated July 18, 2001, issued in connection with the aboveidentified application.
- 3. It is my belief that one of ordinary skill in the art would appreciate that the above identified application identifies substantial and specific utilities for the protein of the above-identified application, DNA encoding the protein,

and antibodies which react with and are specific to at least one epitope included in the described protein. I believe one of ordinary skill in the art would appreciate that the above-identified application identifies, for example, at least the following substantial and specific utilities for the disclosed subject matter: methods and treatment of male infertility, such as has been caused by protein metabolism disturbances in the epididymis, and compounds and compositions to perform these methods.

- 4. To demonstrate the utility of the disclosed subject matter, I have performed, or had performed at my direction, the following experiments.
- 5. Specifically, the experiments described herein were performed to demonstrate a utility for the disclosed human receptor protein designated HE6 and antibodies against this protein. The human receptor protein HE6 has the amino acid sequence shown in SEQ ID NO:2 of the above-identified application.
- 6. The following data derived from knockout (i.e., KO) mouse. Specifically a knockout mouse was developed, wherein the murine counterpart of the human HE6 sequence was deleted. The results obtained in the mouse model also show that the human HE6 receptor is useful as a male-specific contraceptive target.

The following outlines the data presented herinafter and attached:

- A. Construction of the knock out
- B. Verification of the knock out
- C. Knock out phenotype
 - C.1. Fertility phenotype/mating experiments
 - C.2. Spermatozoa phenotype

A. Construction of the knock out mouse

A knock out construction was generated using the exon/intron regions upstream of the beginning of the first transmembrane region and downstream of the seven transmembrane domain (7TM) for recombination (see fig.1). After successful recombination the whole 7TM of the murine counterpart of HE6 was deleted. The disrupted 7TM locus was replaced by a beta-galactosidase gene cassette (knock in), allowing the easy monitoring of the expression by means of simple X-Gal staining. LacZ was to be expressed expressed according to the HE6 expression pattern under control of the endogenous HE6 promotor.

Two positive HE6 KO lines (embryonic stem cell line E14) called A78 and A85 have been injected into C57/B16 blastocysts. After reimplantation into pseudopregnant females chimera animals have been obtained. Those with transmitted KO-construct into the germ line have been confirmed by PCR analysis (fig.2). The chimera males were than crossed with wild type

(WT) B16 female mice to produce heterozygous mice. Heterozygous females were mated with WT males to obtain hemizygous KO males with total loss of HE6. The HE6 gene had been mapped previously on the X chromosome in human. Some time later HE6 could be found in public domain databases mapped on position Xp21.3

No apparent lethality of HE6 knock out mice has been found. The relationship between born KO and WT males was as predicted by the Mendel law (fig. 3).

Two independent lines of HE6 KO mice, A78 and A85, have been derived and are used for fertility studies.

B. Verification of the knock out

Using the seven transmembrane region as a probe in the Northern blot no signal was observed in KO mouse (fig. 4).

HE6 protein can be localized by using specific polyclonal antisera derived from the immunization of rabbits with an N-terminal HE6 peptide. HE6 protein is present in WT mice on the kinocilia of epithelial cells of the ductuli efferentes and on the stereocilia of epithelial cells of the initial segment, the caput and partly on the corpus of the epididymis (fig. 9-16). Antibodies against the sequences of the present application therefore were used, as described in the present application, to analyze fertility. In HE6 KO

mice no kinocilia or stereocilia staining was recognizable with the antisera. The preimmune controls were also included.

In addition, the absence of the HE6 protein in KO mice was shown by Western blot analysis (fig. 5)

C. Knock out phenotype

Hemizygous KO males appeared normal and showed no obvious behavioral phenotype. Weight and size of the KO mice were comparable to WT mice. The organ weights of testis, epididymis, seminal vesicle, prostate, kidney, brain, spleen and heart were analyzed. No obvious differences were found when comparing eight KO with eight WT animals of the same litter. Only the weight of the epididymis is significantly reduced in KO male mice (fig. 6).

C.1 Fertility phenotype

The recent data from all the mating experiments is summarized in the attached Table 1. Sixteen KO mice derived from the A78 founder line and six KO mice from the A85 clone have been analyzed in up to three mating experiments.

Results with A78 KO mice: Animals aged up to nine weeks were infertile in 4 out of 13 experiments. In three cases they were dramatically subfertile (litters only one). Nine to twelve week old animals were infertile in

10 out of 15 experiments. Adult mice older than twelve weeks were infertile. in 9 out of 13 experiments.

Results with A85 KO mice: similar results as seen with the A78 founder were obtained with the A85 KO mouse. Half of all animals up to 12 weeks were infertile (3/6). In experiments with mice older than 12 weeks 4 out of 6 were infertile.

These results clearly demonstrate that the function of HE6 is essential for male fertility. Even subadult animals have significantly reduced fertility. With increasing age KO mice tend to be infertile.

C.2 Spermatozoa phenotype

Spermatoza from the cauda epididymis were analyzed. In every case a prominent phenotype was observed. The sperm count was dramatically reduced. About 20% of the normal number of spermatozoa was found (fig.7). The observed motility is estimated at 0 and 1 according to the WHO-categorization.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false tatements may jeopardize the validity of the application or any patent issuing thereon.

Dr. Ulrich Gottwald

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